We claim

1. An improved industrial process for manufacture of metoprolol base and salts thereof, wherein, the said process comprises of

    a) preparation of metoprolol base and

    b) preparation of metoprolol salts

wherein, the said process for the preparation metorpolol base comprises,

i) preparation of epoxide by reacting 4-(2-methoxy ethyl) phenol and epichlorohydrin in aqueous media like water, in presence of inorganic base such as sodium hydroxide at a temperature range of 10 - 45°C upto more than 3 hours,

separating the aqueous phases and organic phases at the end of the reaction,

washing the organic phase repeatedly with water, maintaining the pH between 7-8,

removing the traces of water from organic phase by azeotropic distillation under vacuum below 55° C for 3-5 hours and

drying the residue at 55° C under vacuum for 3 to 5 hours, to achieve the high purity and further

ii) conversion of the epoxide into metoprolol base by treating with isopropyl amine in aqueous media like water at temperature 0-30° C upto 3 hours,

cooling the reaction mass to 0-5° C to achieve the high purity,

quenching the reaction mass with water,

extracting the product with toluene,

washing the toluene layer with water,

removing the traces of isopropyl amine under vacuum below 25°C to avoid the formation of impurity in the product and

distilling out toluene under vacuum at temperature 30 – 40°C to obtain metoprolol base in high yield and purity,

and wherein the said process for preparation of metoprolol salts more specifically metoprolol succinate salt comprises

i) dissolving the metoprolol base in seven volumes of acetone and heated at 45°C,

ii) after charcoalization filter the said reaction mixture at 45°C,

iii) the said reaction mass is heated to reflux,

iv) preparing the solution of succinic acid in stoicheometric proportion to metoprolol in 1:2 ratio in twenty volumes of acetone by refluxing,

v) adding the succinic acid solution to metoprolol base solution by adjusting the pH of the said reaction mixture at 7.1-7.3,

vi) refluxing the reaction mixture for 4-5 hours,

vii) cooling the reaction mixture to 26° C,

viii) maintaining the same temperature of the reaction mixture with stirring for two hours,

ix) filtering the metoprolol succinate salt,

x) crystallizing the metoprolol succinate salt and

xi) purifying metoprolol succinate salt with three volume of methanol to obtain the (Stoicheometric)yield 72-75% with a purity of 99.8% ,

and wherein the said process for preparation of metoprolol salt more specifically metoprolol tartarate salt comprises

i) dissolving the metoprolol base in seven volumes of acetone,

ii) adding the activated charcoal,

iii) heating to 45°C,

iv) stirring for 30 minutes,

v) filtering the charcoal,

vi) preparing the solution of tartaric acid in acetone by dissolving tartaric acid in stoicheometric proportion of 1:2 (metoprolol base) in 18 volumes of acetone by refluxing,

vii) adding the tartaric acid solution to metoprolol base solution under refluxing condition by adjusting the pH between 6.1-6.3,

viii) refluxing the reaction mixture for 4 hours,

ix) cooling to 26°C,

x) stirring the reaction mixture at 26°C for 2 hours,

xi) filtering the metoprolol tartrate and

xii) the metoprolol tartrate is crystallized from nine volumes of isopropyl alcohol to obtain (Stoicheometric) yield 72-73% with purity 99.8% by HPLC.

2. An improved industrial process for manufacture of metoprolol base as claimed in claim 1 wherein the molar ratio of 4-(2-methoxyethyl) phenol to epichlorohydrin is in the range of 1:0.92 to 1:2.0.

3. An improved industrial process for manufacture of metoprolol base as claimed in claim 1 wherein the molar ratio of 4 (2-methoxyethyl) phenols to epichlorohydrin is in the range of 1:1.1 to 1:1.4.

4. An improved industrial process for manufacture of metoprolol base as claimed in claim 1 wherein the molar ratio of 4(2-methoxyethyl)phenol to epichlorohydrin is in the ratio of 1:1.31

5. An improved industrial process for manufacture of metoprolol base as claimed in claim 1 wherein the molar ratio of sodium hydroxide to 4-(2-methoxyethyl) phenol is used in the range of 1.14:0.95 to 1.024:1.0.

6. An improved industrial process for manufacture of metoprolol base as claimed in claim 1 wherein the molar ratio of sodium hydroxide to 4-(2-methoxyethyl) phenol is used in the ratio of 1.136:1.

7. An improved industrial process for manufacture of metoprolol base as claimed in claim 1 wherein concentration of sodium hydroxide in water is 25% w/v.

8. An improved industrial process for manufacture of metoprolol base as claimed in claim 1 wherein the molar ratio of 4-(2-methoxyethyl) phenol : water is 1:6 volumes.

9. An improved industrial process for manufacture of metoprolol base as claimed in claim 1 wherein the said reaction is carried out in the temperature range of 40 to 45° C.

10. An improved industrial process for manufacture of metoprolol base as claimed in claim 1 wherein temperature during the addition of epoxide to isopropyl amine is 10° to 25°C.

11. An improved industrial process for manufacture of metoprolol base as claimed in claim 1 wherein the temperature for completion of reaction is 30°C in 3hours.

12. An improved industrial process for manufacture of metoprolol base as claimed in claim 1 wherein molar ratio of epoxide : isopropyl amine is 1 : 5.0 – 5.5.

13. An improved industrial process for manufacture of metoprolol base as claimed in claim 1 wherein molar ratio of epoixde: isopropyl amine is 1: 5.2 - 5.3.

14. An improved industrial process for manufacture of metoprolol base as claimed in claim 1 wherein ratio of water to epoxide is 2: 1 vol : wt.

15. An improved industrial process for manufacture of metoprolol base as claimed in claim 1 wherein the reaction mass is quenched with 2.25 volume of water and the product is extracted by 3 volumes of toluene.

17. An improved industrial process for manufacture of metoprolol base as claimed in claim1 wherein the toluene layer is washed 1 to 5 times with water to remove isopropylamine content to less than 0.5%.

18. An improved industrial process for manufacture of metoprolol base as claimed in claim 1 wherein toluene is distilled out under vacuum at temperature 30– 40°C to obtain metoprolol base.

20. An improved industrial process for manufacture of metoprolol base and salts thereof claimed in claim 1 wherein metoprolol salts obtained by the claimed process have no impurity more than 0.1 %

21. An improved industrial process for manufacture of metoprolol base and salts thereof substantially described herein with reference to the foregoing examples.

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